IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PURDUE PHARMA PRODUCTS L.P., NAPP PHARMACEUTICAL GROUP LTD., BIOVAIL LABORATORIES INTERNATIONAL, SRL, and ORTHO-MCNEIL, INC., Plaintiffs/Counterclaim-defendants, v. PAR PHARMACEUTICAL, INC. and PAR PHARMACEUTICAL COMPANIES, INC., Defendants/Counterclaim-plaintiffs.	C.A. No. 07-255-JJF (CONSOLIDATED)

PLAINTIFFS' OPENING BRIEF ON CLAIM CONSTRUCTION

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I. NATURE AND STAGE OF THE PROCEEDINGS

Pursuant to paragraph 6 of the Joint Order of Consolidation and Rule 16 Scheduling Order (D.I. 23), Plaintiffs submit this opening brief on claim construction in this action for relief from infringement of U.S. Patents Nos. 6,254,887 ("'887 patent") (Whitney Ex.[1] 1) and 7,074,430 ("'430 patent") (Whitney Ex. 2).

II. SUMMARY OF ARGUMENT

1. When construing the claims of the patent, the Court considers the literal language of the claims, the patent specification and the prosecution history. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979-80 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996). The specification is usually dispositive; "'it is the single best guide to the meaning of a disputed term.'" *Phillips v. AWH Corp.*, 415 F.3d 1303, 1315 (Fed. Cir. 2005) (en banc) (*quoting Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996)).

2. Absent a specific definition based on the context of the claim language and the patent specification, the Court should interpret the language by applying the ordinary and accustomed meaning of the words in the claim. *See Phillips*, 415 F.3d at 1316. It is improper to import limitations into a claim that are not required by the context of the claim read in light of the intrinsic evidence, *i.e.*, the claims, specification and prosecution history. *Id.* at 1323-24.

3. The patents in suit disclose and claim controlled release formulations of tramadol, a non-steroidal analgesic used to treat moderate to severe pain. The parties have agreed on the constructions of three claim terms as set forth in the following table.

[1] "Whitney Ex. ___" refers to the Declaration of Reeta K. Whitney in Support of Plaintiffs' Opening Brief on Claim Construction filed concurrently herewith.

CLAIM TERM	AGREED UPON CLAIM CONSTRUCTION
controlled release coating	A coating that achieves slow release of a drug over an extended period of time, thereby extending the duration of drug action over that achieved by conventional delivery.
substrate	A solid pharmaceutical preparation that contains the active ingredient.
W_{50}	The width of the plasma profile at 50% C_{max}, *i.e.*, the duration over which the plasma concentrations are equal to or greater than 50% of the peak concentration.

4. There are six claim terms in dispute: "therapeutic effect," "matrix," "normal release matrix," "a pharmaceutically effective amount of tramadol or a salt thereof," "therapeutic effect for about 24 hours after oral administration," and "therapeutic effect for at least about 24 hours after administration." The proposed constructions of the parties are set forth in the following table, and for ease of reference, in Attachment A attached hereto. Plaintiffs' proposed constructions of these terms comport with the legal principles set forth in the controlling authorities. Defendants' do not.

DISPUTED CLAIM TERM	PLAINTIFFS' PROPOSED CLAIM CONSTRUCTIONS	DEFENDANTS' PROPOSED CLAIM CONSTRUCTIONS
therapeutic effect	Effective for the treatment of one or more clinical conditions, *e.g.*, pain.	The controlled release oral pharmaceutical preparation must cause analgesic efficacy in human patients experiencing pain as demonstrated by scientifically valid placebo-controlled clinical evidence.

DISPUTED CLAIM TERM	PLAINTIFFS' PROPOSED CLAIM CONSTRUCTIONS	DEFENDANTS' PROPOSED CLAIM CONSTRUCTIONS
matrix	A pharmaceutical preparation that incorporates the active ingredient dispersed within a solid dosage form.	A system wherein a drug is incorporated into a polymer(s) structure by either particle or molecular dispersion, wherein the former is a suspension of drug particles homogenously distributed in the polymer(s) structure and in the latter drug molecules are dissolved in the polymer, and wherein drug release occurs by diffusion through and/or erosion of the polymer structure.
normal release matrix	A matrix that does not substantially slow the release of the active ingredient.	A matrix that does not slow the release of the active ingredient.
a pharmaceutically effective amount of tramadol or a salt thereof	An amount of tramadol or its salt sufficient to provide at least some analgesia.	An amount of tramadol or its salt contained in the substrate or the normal release matrix to achieve a therapeutic effect.
therapeutic effect for about 24 hours after oral administration	Effective for the treatment of one or more clinical conditions, *e.g.*, pain, for about 24 hours after oral administration.	The controlled release oral pharmaceutical preparation must cause analgesic efficacy in human patients experiencing pain as demonstrated by scientifically valid placebo-controlled clinical evidence and subsequent to oral administration of a dose of the preparation the analgesic efficacy in the patients must last for a period of about 24 hours from the time of onset of action.
therapeutic effect for at least about 24 hours	Effective for the treatment of one or more clinical conditions, *e.g.*, pain, for at least about 24 hours.	The controlled release oral pharmaceutical preparation must cause analgesic efficacy in human patients experiencing pain as demonstrated by scientifically valid placebo-controlled clinical evidence and subsequent to oral administration of a dose of the preparation the analgesic efficacy in the patients must last for a period of about 24 hours from the time of onset of action.

III. STATEMENT OF FACTS

A. Background

1. The Parties

Plaintiffs Purdue Pharma Products L.P. ("Purdue") and Napp Pharmaceutical Group Ltd. ("Napp") are commonly owned, associated companies. Purdue and Napp are joint owners by assignment of the two patents in suit. (D.I. 78).

Plaintiff Biovail Laboratories International, SRL ("Biovail") is the holder of the New Drug Application ("NDA") for the branded controlled release tramadol formulation that is approved by the Food and Drug Administration ("FDA") and sold in the United States as ULTRAM® ER. (*Id.*). Plaintiff Ortho-McNeil, Inc. ("Ortho") markets ULTRAM® ER in the United States. (*Id.*).

Defendants Par Pharmaceutical, Inc. and Par Pharmaceutical Companies, Inc. (collectively "Par") have filed an abbreviated new drug application ("ANDA") for FDA approval to make generic copies of ULTRAM® ER in various dosage strengths. (*Id.*).

2. The Patented Technology

(a) Tramadol and Immediate Release Formulations

Tramadol is an analgesic, a drug that relieves pain, such as pain from arthritis. It has properties of non-steroidal anti-inflammatory agents (NSAIDs) and properties of opioid analgesics. (Davies ¶ 18).[2]

Tramadol was known in various immediate release formulations before the inventions of the patents in suit. Immediate release formulations are those in which the drug is administered with the goal of having the entire dose of active ingredient enter the patient's

[2] "Davies ¶ ___" refers to the Declaration of Dr. Martyn C. Davies in Support of Plaintiffs' Opening Brief on Claim Construction filed concurrently herewith.

bloodstream as quickly as feasible. For drugs administered orally, this usually means a dosage form that dissolves in the patient's stomach within minutes. (Davies ¶ 19).

(b) Controlled Release Technology

A controlled release dosage form is one in which the active ingredient is released in a controlled manner, *e.g.*, (1) at a predetermined rate, *e.g.*, so much in the first hour, so much in the second hour, etc.; (2) at a predetermined time, *e.g.*, x minutes or hours after administration; or (3) in a predetermined place or under predetermined conditions of pH, *e.g.*, in the patient's small intestine, where the fluids are more alkaline, as opposed to the stomach, where the fluids are more acidic. (Davies ¶ 20). One of the advantages of a controlled release dosage form is that it extends the duration of drug action of the active ingredient over that achieved by immediate release formulations. (Whitney Ex. 1, 1:34-37).

Controlled release technology is inherently complex. Among the factors that must be balanced are the chemistry of the inert ingredients ("excipients") used as a controlled release mechanism; the chemistry of the digestive system, which changes as one moves from the stomach to the intestines; the chemistry of the active ingredient, *e.g.*, how quickly it dissolves; how the body chemistry works on the dosage form and the active ingredient ("pharmacokinetics"); and how the dosage form ultimately works on the body ("pharmacodynamics"). (Davies ¶ 21).

The patents in suit disclose different controlled release mechanisms useful in an orally administered dosage form in which tramadol is the active ingredient, *infra* pp. 7-11.

(c) The Drug Development Process

Drug development is costly and time consuming. Each successive step of the process requires increased resources, including funds and manpower, from the company sponsoring the development. (Smith ¶ 5).[3]

The first step is to identify a suitable active ingredient and a target for how that active ingredient will behave when administered to patients. Following that, an iterative process begins between the chemists who attempt to develop a formulation ("formulators") to meet those goals and the other scientists and doctors ("clinicians") responsible for determining whether an experimental formulation is safe for testing on humans and whether it shows sufficient promise to proceed to the next stage of development. (Smith ¶ 6).

The iterative process begins with *in vitro* testing. The experimental formulation is tested in fluids and under conditions that simulate to some extent the chemistry of the stomach and intestine. The amount of the active ingredient in the laboratory sample can be measured over time as it dissolves. This is sometimes called the "dissolution profile" for the formulation. *In vitro* testing identifies formulations that are suitable candidates for testing in humans. The formulators and clinicians repeat this process until a suitably promising test formulation is created. (Davies ¶¶ 22-24).

Clinical testing in humans is called *in vivo* testing. One type of *in vivo* test measures the blood plasma level of the active ingredient in healthy test subjects over a period of time after dosing. This is called "bioavailability" testing. If the formulation fails bioavailability testing, the iterative process of re-formulation and *in vitro* testing begins again. If a formulation

[3] "Smith ¶___" refers to the Declaration of Kevin J. Smith in Support of Plaintiffs' Opening Brief on Claim Construction filed concurrently herewith.

provides the target blood plasma levels, then the company may decide to commit resources to proceed to later stages of clinical trials. (Smith ¶ 7).

(d) The Making of the Inventions of the Patents in Suit

Scientists at Mundipharma GmbH ("Mundipharma"), a German company associated with Purdue and Napp, first identified tramadol as a possible active ingredient for use in a controlled release formulation. Mundipharma began work on a controlled release tramadol formulation in the early 1990s. Their efforts initially focused on a 12-hour formulation. A 12-hour formulation is one that can provide therapeutic effect when administered twice daily. This was an advantage over immediate release tramadol formulations, which were administered four times daily. (Smith ¶¶ 8-9). Initial *in vivo* testing of this formulation was supported by clinicians at Napp. (Smith ¶ 9). Early in this development project, scientists at Napp proposed a 24-hour formulation. This proposal included a target blood plasma profile, and an estimate of the *in vitro* dissolution ranges that might produce the target profile. (Smith ¶ 10). Work at Napp proceeded on this formulation. (Smith ¶ 10).

B. The Patents In Suit

1. The Priority Applications

Four foreign patent applications were filed between May 10, 1993 and March 14, 1994 disclosing this work. On May 10, 1994, these applications were combined into a single U.S. patent application, naming five co-inventors from Napp and three from Mundipharma. This application issued as U.S. Patent No. 5,591,452 ("'452 patent"). The '887 patent in suit is a divisional of the '452 patent.

2. '887 and '430 Share a Common Disclosure

The '887 patent is titled "Controlled Release Tramadol" and the '430 patent is titled "Controlled Release Tramadol Tramadol [sic] Formulation." The '887 patent issued on

July 3, 2001. (Whitney Ex. 1, cover page). The '430 patent is a continuation of the '887 application, having the same specification but different claims. (Whitney Ex. 2, cover page). The '430 patent issued on July 11, 2006 based on an application filed March 6, 2001. (*Id.*).

The '887 patent acknowledges that "[c]onventional release preparations . . . containing tramadol, or more particularly its hydrochloride salt, have been commercially available for many years for use in the treatment of moderate to severe pain; Such preparations, however, do not provide a controlled release of the tramadol." (Whitney Ex. 1, 1:12-18).

The '887 patent states that an object of the invention is to "provide an oral controlled release tramadol preparation suitable for at least twelve-hourly (*e.g.*, up to twenty-four hourly) administration for the treatment of pain." (*Id*., 1:22-25).

The patent next sets forth ranges of *in vitro* dissolution values believed to be useful for 12 and 24 hour formulations based on this research. (*Id.*, 1:41-2:67). Suitable formulations are also disclosed in terms of certain pharmacokinetic parameters: C_{max} (the mean maximum blood plasma concentration), T_{max} (the mean time at which C_{max} occurs) and "W_{50}." "W_{50}" refers to how long (*i.e.*, the "width" of the time period in which) the blood plasma concentrations are equal to or greater than 50% of C_{max}. (*Id.*, 3:1-15). The patent explains a preferred method for measuring *in vitro* dissolution. (*Id.*, 3:16-20).

The patent broadly discloses controlled release mechanisms that are suitable for use in the invention: "The controlled release preparation according to the invention may be presented, for example, as granules, spheroids, pellets, multiparticulates, capsules, tablets, sachets, controlled release suspensions, or in any other suitable dosage form incorporating such granules, spheroids, pellets or multiparticulates." (*Id*., 3:33-38).

The disclosure continues with a description of one particular type of controlled release formulation, a "matrix," which is understood in the art to be a solid dosage form in which the active ingredient is dispersed. (Davies ¶¶ 33-35). The patent describes two types of suitable matrices: "Preferably the matrix is a controlled release matrix. Alternatively, normal release matrices having a coating which provides for controlled release of the active ingredient may be used." (Whitney Ex. 1, 3:44-47). The disclosure goes on to describe various controlled release matrices, and refers again to the alternative of "a normal release matrix having a controlled release coating." (*Id.*, 4:24-28).

The disclosure next sets forth various methods of making a suitable controlled release formulation. (*Id.*, 4:60-7:19, 7:42-51). Suitable additional inert ingredients ("excipients") are also identified. (*Id.*, 7:20-7:41). The inventors also give general guidelines under which the release profile of the active ingredient can be adjusted. (*Id*., 7:52-65).

The '887 patent discloses eight specific examples of formulations, and provides *in vitro* dissolution data for all eight. (*Id.*, 8:14-12:9). Two of these formulations were clinically tested *in vivo* to determine whether they provided the target blood plasma levels. The results of those clinical tests are reported in the patent drawings, Figures 1 and 2. (*Id.*, 9:51-53; 12:11-15; FIGs. 1 and 2).

The '430 patent is a continuation of the application that issued as '887. Thus, it has the same specification, with slightly different line numbering. (*See* Whitney Ex. 2).

3. Illustrative Claims

Plaintiffs assert that Par's proposed generic copy of ULTRAM® ER, if approved by the FDA, would infringe claims 1, 3, 13, 15, 16, 19, 23, 27, 29 and 31 of the '887 patent and claims 1, 3, 5, 6, 7, 11, 12, 13, 14 and 15 of the '430 patent. Claim 1 of each patent is illustrative. Claim 1 of the '887 patent calls for a controlled release tramadol formulation

including a "substrate coated with a controlled release coating," meeting certain *in vitro* dissolution ranges when tested under certain identified conditions, and "providing a therapeutic effect for about 24 hours after oral administration." '887 Claim 1, with the disputed terms highlighted, states:

> 1. A controlled release oral pharmaceutical preparation suitable for dosing every 24 hours comprising
>
> a substrate comprising **a pharmaceutically effective amount of tramadol or a salt thereof**;
>
> said substrate coated with a controlled release coating;
>
> said preparation having a dissolution rate in vitro when measured using the Ph. Eur. Paddle Method at 100 rpm in 900 ml 0,1 N hydrochloric acid at 37º C. and using UV detection at 270 nm, between 0 and 50% tramadol released after 1 hour; between 0 and 75% tramadol released after 2 hours; between 3 and 95% tramadol released after 4 hours; between 10 and 100% tramadol released after 8 hours; between 20 and 100% tramadol released after 12 hours; between 30 and 100% tramadol released after 16 hours; between 50 and 100% tramadol released after 24 hours; and greater than 80% tramadol released after 36 hours, by weight, said preparation providing a **therapeutic effect for about 24 hours after oral administration**.

(Whitney Ex. 1, 12:16-34). Asserted '887 claims 3, 16 and 27 depend from claim 1 and include further limitations to the controlled release pharmaceutical preparations of claim 1. Asserted claims 13 and 19 are independent claims that are similar to claim 1. '887 claims 15 and 29 depend from claim 13 and include further limitations to the controlled release tablet of claim 13. Asserted claims 23 and 31 depend from claim 19 and include further limitations to the controlled release pharmaceutical preparations of claim 19.

Claim 1 of the '430 patent is similar to '887 claim 1, but eliminates the recitation of the dissolution ranges. Again with the disputed terms highlighted, '430 claim 1 states:

1. A solid controlled release oral dosage form, comprising,

a therapeutically effective amount of tramadol or a pharmaceutically acceptable salt thereof incorporated into a **normal release matrix**,

said **matrix** overcoated with a controlled release coating comprising a polymethacrylate or a water insoluble cellulose,

said dosage form providing a **therapeutic effect for at least about 24 hours**.

(Whitney Ex. 2, 12:41-50). Asserted '430 claims 3, 5, 6, 7, 11, 12, 13, 14 and 15 depend from claim 1 and include further limitations with respect to the composition of the controlled release coating, the amount of tramadol in the dosage form, and the dissolution ranges of the controlled release dosage form.

IV. THE CONTROLLING AUTHORITIES

Claim construction is a question of law. *Markman*, 52 F.3d at 979. Claim terms should be accorded their ordinary and customary meaning unless the patentees "clearly set forth a definition of the disputed claim term in either the specification or prosecution history." *CCS Fitness, Inc. v. Brunswick Corp.*, 288 F.3d 1359, 1366 (Fed. Cir. 2002). The ordinary and customary meaning of a claim term refers to the meaning a person of ordinary skill in the art in question would attach to the term at the time of the invention. *Phillips*, 415 F.3d at 1313. Where the words of the claim are readily apparent, "claim construction . . . involves little more than the application of the widely accepted meaning of commonly understood words." *Id.* at 1314.

The claim construction analysis begins with the words of the claim. *See Phillips*, 415 F.3d at 1312. Claims "must be read in view of the specification, of which they are a part." *Markman*, 52 F.3d at 979. The specification "'is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term.'" *Phillips*, 415 F.3d at 1315 (*quoting Vitronics*, 90 F.3d at 1582). A court must also consider the prosecution history. However, absent a clear and unmistakable disavowal of claim scope, the

claim terms must be accorded their plain and ordinary meaning. *Sorensen v. Int'l Trade Comm'n*, 427 F.3d 1375, 1378-79 (Fed. Cir. 2005). The Court may also consider extrinsic evidence such as technical dictionaries and expert declarations to inform the Court's analysis to the extent that such evidence is consistent with the intrinsic evidence. *Phillips*, 415 F.3d at 1318.

V. PLAINTIFFS' PROPOSED CONSTRUCTION OF THE CLAIM ELEMENTS SHOULD BE ADOPTED

There are six claim terms in dispute. Plaintiffs' proposed claim constructions fairly reflect the terms' plain and ordinary meanings to one of ordinary skill in the art, and are consistent with their use in the specification of the patents in suit to achieve the fundamental purposes of the claimed inventions, as required by the controlling authorities, *supra* pp. 11-12. In contrast, Par's proposed constructions are inconsistent with the plain and ordinary meaning of the disputed term or improperly seek to limit the claims.

A. The Level of Ordinary Skill in the Art

The relevant fields of technology for the patents in suit are drug dosage formulation and the clinical testing of those formulations. For the purposes of claim construction, one of ordinary skill in the art would be a person having a degree in one or more of the fields of medicine, chemical engineering, chemistry, pharmaceutical sciences, pharmaceutics, pharmaceutical technology, pharmacokinetics and/or pharmacology and/or industry training. (Davies ¶¶ 11, 14).

B. "Therapeutic Effect"

PLAINTIFFS' PROPOSED CLAIM CONSTRUCTION	PAR'S PROPOSED CLAIM CONSTRUCTION
Effective for the treatment of one or more clinical conditions, *e.g.*, pain.	The controlled release oral pharmaceutical preparation must cause analgesic efficacy in human patients experiencing pain as demonstrated by scientifically valid placebo-controlled clinical evidence.

"Therapeutic effect" appears in claims 1, 7, 13, 14 and 19 of the '887 patent and claim 1 of the '430 patent. The plain meaning of "therapeutic effect" is informed by the purpose of the patents in suit, which is to provide controlled release tramadol formulations for the treatment of pain. (*See* Whitney Ex. 1, 1:22-25 ("It is an object of the present invention to provide an oral controlled release tramadol preparation suitable for at least twelve-hourly (*e.g.* up to twenty-four hourly) administration for the treatment of pain.")).[4] "Therapeutic effect" would be understood by one of ordinary skill in the art to have its plain and ordinary meaning -- effective for the treatment of one or more clinical conditions, in this case, pain. (Davies ¶¶ 29-32).

The specification is consistent with Plaintiffs' proposed plain meaning construction. The specification states that: "Preferably such a preparation [according to the present invention] maintains a drug concentration in the blood within the therapeutic range for 12 hours or more." (Whitney Ex. 1, 1:38-40). The specification also discloses specific *in vitro* dissolution and *in vivo* plasma profiles. (*See id.*, 1:48-3:4; FIGs. 1 and 2). In addition, the specification describes *in vivo* parameters and the results from the administration of described embodiments in humans. (*See* Whitney Ex. 1, 3:4-15; 8:5-12; Example 3, 9:20-53; Example 8, 11:35-12:14). All of these passages would be understood by one of ordinary skill to characterize the potential for "therapeutic effect." (Davies ¶¶ 31-32).

Par seeks improperly to limit "therapeutic effect" to "analgesic efficacy in human patients experiencing pain as demonstrated by scientifically valid placebo-controlled clinical evidence," or in other words, to require a placebo-controlled clinical trial. This has no basis in the specification or prosecution histories of the patents in suit. Par's proposal imports a

[4] The technical dictionary definition of "therapeutic" is also instructive. "Therapeutic" simply means "the treatment of disease." (Whitney Ex. 3).

limitation that seems to stem from FDA requirements for approval of a new drug formulation. *See* 21 U.S.C. § 355(b)(1)(A). This is irrelevant. There is no similar requirement for a proposed generic copy seeking approval through an Abbreviated New Drug Application ("ANDA"). An ANDA shows efficacy by proving, *inter alia*, bioequivalency to the "listed" innovator drug. *See* 21 U.S.C. § 355(j)(2)(A)(iv).

Neither the claims, the specification nor the file histories of the patents in suit limit "therapeutic effect" to a placebo-controlled clinical trial. It would be improper for the Court to read such limitations into the claims, with no support in the intrinsic evidence. *Burke, Inc. v. Bruno Indep. Living Aids, Inc.*, 183 F.3d 1334, 1340-41 (Fed. Cir. 1999). Par's construction is inconsistent with the intrinsic evidence and contrary to law.

Plaintiffs' proposed construction fairly construes "therapeutic effect" when viewed in the context of the claims, specification, and prosecution histories. The Court should adopt Plaintiffs' proposed construction.

C. "Matrix"

PLAINTIFFS' PROPOSED CLAIM CONSTRUCTION	PAR'S PROPOSED CLAIM CONSTRUCTION
A pharmaceutical preparation that incorporates the active ingredient dispersed within a solid dosage form.	A system wherein a drug is incorporated into a polymer(s) structure by either particle or molecular dispersion, wherein the former is a suspension of drug particles homogenously distributed in the polymer(s) structure and in the latter drug molecules are dissolved in the polymer, and wherein drug release occurs by diffusion through and/or erosion of the polymer structure.

The term "matrix" appears in the claim phrases "normal release matrix" and "said matrix [referring back to the normal release matrix] overcoated with a controlled release coating" in claim 1 of the '430 patent. Claim 1 is reproduced below:

> 1. A solid controlled release oral dosage form, comprising,
>
> a therapeutically effective amount of tramadol or a pharmaceutically acceptable salt thereof incorporated into a **normal release matrix**,
>
> **said matrix** overcoated with a controlled release coating comprising a polymethacrylate or a water insoluble cellulose,
>
> said dosage form providing a therapeutic effect for at least about 24 hours.

(Whitney Ex. 2, 12:41-50).

When read in the context of the intrinsic evidence, one of ordinary skill in the art would understand "matrix" to mean a pharmaceutical preparation that incorporates the active ingredient dispersed within a solid dosage form. (Davies ¶¶ 33-35).

Plaintiffs' construction of "matrix," consistent with the claim language, permits the matrix to be a normal release matrix or a controlled release matrix. The '430 patent claims further specify that the matrix is a "normal release matrix." Accordingly, in the context of claim construction, the definition of "matrix" must be broad enough to encompass both types, otherwise the phrase "normal release" would be superfluous. The rest of the intrinsic record comports with Plaintiffs' construction. The specification discloses normal and controlled release matrices. (*See, e.g.*, Whitney Ex. 1, 3:39-47; 4:24-28). Accordingly, Plaintiffs' proposed construction also encompasses, in addition to matrices that incorporate classic hydrophilic polymers, matrices disclosed in the specification that incorporate digestible long chain substituted or unsubstituted hydrocarbons, *e.g.*, waxes and vegetable oils, as well as other pharmaceutically acceptable ingredients. (Davies ¶ 34; *see, e.g.*, Whitney Ex. 1, 3:48-4:19).

Plaintiffs' proposed construction is also consistent with the prosecution history. Claim 1 of the '430 patent originally read:

> 1. (Amended) A solid controlled release oral dosage form, comprising a therapeutically effective amount of tramadol or a pharmaceutically acceptable salt

> thereof incorporated into a matrix, said dosage form providing a therapeutic effect for at least about 24 hours.

(Whitney Ex. 4, paper #5 at p. 2). The PTO rejected that claim in light of two references, Bondi and Raffa.[5] Subsequent to three PTO rejections over the same references, the applicants amended claim 1 to insert two additional limitations:

> 1. (currently amended): A solid controlled release oral dosage form, comprising,
>
> a therapeutically effective amount of tramadol or a pharmaceutically acceptable salt thereof incorporated into a normal release matrix,
>
> said matrix overcoated with a controlled release coating comprising a polymethacrylate or a water insoluble cellulose,
>
> said dosage form providing a therapeutic effect for at least 24 hours.

(*Id.*, Jan. 12, 2005 Amendment at p. 2; *see also* Whitney Ex. 4, papers 9, 14 and 17). The purpose of the amendment was to explain to the PTO that in the '430 claims, the controlled release function was provided by a polymethacrylate or a water insoluble cellulose coating, not by the matrix itself or, as in Bondi, by a membrane comprised of polyvinyl alcohol ("PVA"). (*Id.*) From this amendment, it is plain that in claim 1 the term "matrix" only has meaning as part of the phrase "normal release matrix" and that the matrix is not limited to the polymer structure argued by Par.

Par's proposed construction limits "matrix" to "polymer structures . . . wherein drug release occurs by diffusion through and/or erosion of the polymer structure." Par's proposed construction seeks to limit the meaning of the word "matrix" to a specific type of

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[5] The PTO contended that Raffa et al., *Opioid and Nonopioid Components Independently Contribute to the Mechanism of Action of Tramadol, An 'Atypical' Opioid Analgesic*, J. PHARMACOL. EXP. THER. 260, 275-85 (1992) ("Raffa") discloses the use of tramadol hydrochloride as a pain medicament with opioid and nonopioid properties. The PTO further contended that EP 0 147 780 ("Bondi") discloses a controlled release method for a variety of compounds of which tramadol is listed as an example. (Whitney Ex. 4, paper #6 at p. 2).

matrix, namely a controlled release matrix. (Davies ¶ 35). Nothing in the claim language or the specification requires such a limitation and, thus, it would be improper to add it to the claim. *Phonometrics, Inc. v. N. Telecom Inc.*, 133 F.3d 1459, 1466 (Fed. Cir. 1998). Par's proposed construction of "matrix" would exclude normal release matrices as discussed above. This is the antithesis of the plain language of claim 1 of the '430 patent. The Court should reject Par's proposed construction for this reason alone.

Second, Par's construction excludes embodiments disclosed in the specification, *i.e.*, normal release matrices. (*See, e.g.*, Whitney Ex. 1, 3:45-47; 4:24-55). Such a construction is seldom, if ever, correct. *Pfizer, Inc. v. Teva Pharms. USA, Inc.*, 429 F.3d 1364, 1374 (Fed. Cir. 2005) (*citing SanDisk Corp. v. Memorex Prods., Inc.*, 415 F.3d 1278, 1285 (Fed. Cir. 2005)). In short, nothing in the claim language itself, the specification or the prosecution histories of the patents in suit or their parent supports limiting "matrix" as Par proposes. The Court should adopt Plaintiffs' proposed plain and ordinary meaning construction of "matrix."

D. "Normal Release Matrix"

PLAINTIFFS' PROPOSED CLAIM CONSTRUCTION	PAR'S PROPOSED CLAIM CONSTRUCTION
A matrix that does not substantially slow the release of the active ingredient.	A matrix that does not slow the release of the active ingredient.

The proper construction of "matrix" was addressed *supra* pp. 14-17. The parties' dispute over the construction of "normal release matrix" is whether the proper construction of "normal release matrix" is a matrix "that does not substantially slow the release of the active ingredient" or one that absolutely "does not slow" release. The distinction here is that Plaintiffs' proposal recognizes, as one of ordinary skill in the art would understand, that even in an immediate release formulation, the addition of inert excipients to an active ingredient may incidentally slow the dissolution of the active ingredient to a limited extent. The term "normal

release" matrix is used in the patents in suit to contrast with, and as an alternative to, a "controlled release" matrix, where the release is slowed by design. A normal release matrix will release the active ingredient as quickly as is feasible. (Davies ¶¶ 36-39). Accordingly, the fair import of the claim term is that a "normal release matrix" will not, by itself, substantially slow the release of the active ingredient.

Par's construction of "normal release" attempts to exclude matrices that slow drug release by even an insubstantial amount. If construed Par's way, the claim thus arguably would exclude disclosed embodiments, *i.e.*, normal release matrices. This is improper. *See Pfizer*, 429 F.3d at 1374 (*quoting SanDisk*, 415 F.3d at 1285) (rejecting construction excluding preferred embodiment); *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1362 (Fed. Cir. 2008) (rejecting construction where some claims "would cover nothing"). The Court should adopt Plaintiffs' proposed construction of "normal release matrix."

E. "A Pharmaceutically Effective Amount of Tramadol or a Salt Thereof"

PLAINTIFFS' PROPOSED CLAIM CONSTRUCTION	PAR'S PROPOSED CLAIM CONSTRUCTION
An amount of tramadol or its salt sufficient to provide at least some analgesia	An amount of tramadol or its salt contained in the substrate or the normal release matrix to achieve a therapeutic effect.

The disputed claim term "a pharmaceutically effective amount of tramadol or a salt thereof" is included in claims 1, 13 and 14 of the '887 patent.[6] The claim element of Claim 1 is illustrative: "a substrate comprising a pharmaceutically effective amount of tramadol or a salt thereof." (Whitney Ex. 1, 12:18-19).

[6] Claim 19 of the '887 patent states "a pharmaceutically effective amount of an opioid analgesic consisting essentially of tramadol or a salt thereof."

Plaintiffs' proposed construction is informed by the specification. Tramadol is an orally active analgesic. (*Id.*, 1:10-12). The specification states that the "controlled release preparation according to the invention preferably contains an analgesically effective amount of tramadol or a pharmaceutically acceptable salt thereof . . . ." (*Id.*, 3:27-32). One of ordinary skill in the art would understand that a pharmaceutically effective amount of the active ingredient, tramadol or a salt thereof, would provide at least some analgesia. (Davies ¶¶ 40-43).

Par's construction seeks improperly to limit the claims to an amount of tramadol "contained in the substrate or the normal release matrix to achieve a therapeutic effect." The fundamental flaw in Par's proposal is that it adds a limitation ("normal release matrix") not set forth in the claim itself. This is improper. *Purdue Pharma L.P. v. Endo Pharms. Inc.*, 438 F.3d 1123, 1136-37 (Fed. Cir. 2006). In fact, the only independent claim that actually does contain the phrase "normal release matrix," claim 1 of the '430 patent, does *not* use the term "pharmaceutically effective" amount of tramadol. Rather, it includes the term "a *therapeutically* effective amount of tramadol," a term that is not in dispute. There is no sound reason to import a limitation from one claim into another where it does not appear. *SRI Int'l v. Matsushita Elec. Corp. of Am.*, 775 F.2d 1107, 1122 (Fed. Cir. 1985).

Similarly, Par's proposal incorporates "substrate" into the meaning of the "pharmaceutically effective amount." This is either redundant and unnecessary or it is inconsistent with the plain language of the claims. (Davies ¶ 42). '887 claims 1 and 19 call for "a *substrate* comprising a pharmaceutically effective amount . . . ." Repeating the "substrate" limitation adds nothing to the explicit language of the claim. '887 claims 13 and 14 begin "a *tablet* comprising a pharmaceutically effective amount . . . ." In these claims, adding "substrate or normal release matrix" is inconsistent with the language of the claims. (Davies ¶ 43). In

either case, Par's proposed limitation is improper. *See In re Gabapentin Patent Litig.*, 503 F.3d 1254, 1263 (Fed. Cir. 2007) (rejecting construction rendering claims superfluous); *Ortho-McNeil Pharm.*, 520 F.3d at 1362 (rejecting construction rendering claims meaningless).

To the extent that Par seeks to incorporate its (erroneous) definition of "therapeutic effect" into the definition of "pharmaceutically effective amount," there is no sound reason to do so. Again, there is reference to therapeutic effect elsewhere in each of the claims at issue. This strongly suggests that the meaning of "a pharmaceutically effective amount" is different from providing a "therapeutic effect." It is presumed that different words in a claim mean different things. *Aero Prods. Int'l, Inc. v. Intex Recreation Corp.*, 466 F.3d 1000, 1013 (Fed. Cir. 2006). Par has provided no basis to overcome that presumption; there is no support in the intrinsic evidence for Par's argument.

The Court should adopt Plaintiffs' proposed construction of "a pharmaceutically effective amount of tramadol or a salt thereof."

F. "Therapeutic Effect for About 24 Hours After Oral Administration"

PLAINTIFFS' PROPOSED CLAIM CONSTRUCTION	PAR'S PROPOSED CLAIM CONSTRUCTION
Effective for the treatment of one or more clinical conditions, *e.g.*, pain, for about 24 hours after oral administration.	The controlled release oral pharmaceutical preparation must cause analgesic efficacy in human patients experiencing pain as demonstrated by scientifically valid placebo-controlled clinical evidence and subsequent to oral administration of a dose of the preparation the analgesic efficacy in the patients must last for a period of about 24 hours from the time of onset of action.

The proper construction of "therapeutic effect" was addressed *supra* pp. 12-14. Plaintiffs propose that "for about 24 hours after oral administration" needs no further

construction. These are plain English words. Their meaning is apparent from the context of the intrinsic evidence. (Davies ¶ 44)

Par's attempt to add the requirement of "placebo controlled clinical studies" to the claims is improper for the reasons discussed *supra* pp. 13-14.

Par's proposal would further add the limitation that "about 24 hours after oral administration" be measured in a particular way: "subsequent to oral administration of a dose of the preparation the analgesic efficacy in the patients must last for a period of about 24 hours from the time of onset of action." Nothing in the specification of the patents in suit or in the prosecution histories discusses measuring 24 hours after oral administration from the onset of action. There is no support in the intrinsic evidence for limiting the claim as Par proposes.

Moreover, regardless of when pain relief begins after the *first* dose is taken, the formulations are designed to provide pain relief for "about 24 hours" so that the dosage can be taken only once a day. Adding a claim limitation, unnecessary in any event, that violates the fundamental purpose of the invention is improper. *See Purdue Pharma L.P. v. Boehringer Ingelheim GmbH*, 237 F.3d 1359, 1364 (Fed. Cir. 2001).

The Court should adopt Plaintiffs' plain meaning construction of "therapeutic effect for about 24 hours after oral administration."

G. "Therapeutic Effect for at Least About 24 Hours"

PLAINTIFFS' PROPOSED CLAIM CONSTRUCTION	PAR'S PROPOSED CLAIM CONSTRUCTION
Effective for the treatment of one or more clinical conditions, *e.g.*, pain, for at least about 24 hours.	The controlled release oral pharmaceutical preparation must cause analgesic efficacy in human patients experiencing pain as demonstrated by scientifically valid placebo-controlled clinical evidence and subsequent to oral administration of a dose of the preparation the analgesic efficacy in the patients must last for a period of about 24 hours from the time of onset of action.

"Therapeutic effect for at least about 24 hours" appears in '887 claim 7 and '430 claim 1. For the same reasons as discussed in the preceding section, the Court should adopt Plaintiffs' proposed plain meaning construction.

Par's proposed construction of "about 24 hours" is the same as its construction of "at least about 24 hours." Par's construction would render the plain language of the words "at least" superfluous, contrary to the controlling authorities. *See Aero Prods. Int'l*, 466 F.3d at 1013. Par's construction should be rejected for this additional reason.

VI. CONCLUSION

For the reasons stated above, the Court should adopt Plaintiffs' proposed claim constructions.

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CERTIFICATE OF SERVICE

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TAB A

ATTACHMENT A

DISPUTED CLAIM TERM	PLAINTIFFS' PROPOSED CLAIM CONSTRUCTIONS	DEFENDANTS' PROPOSED CLAIM CONSTRUCTIONS
therapeutic effect	Effective for the treatment of one or more clinical conditions, *e.g.*, pain.	The controlled release oral pharmaceutical preparation must cause analgesic efficacy in human patients experiencing pain as demonstrated by scientifically valid placebo-controlled clinical evidence.
matrix	A pharmaceutical preparation that incorporates the active ingredient dispersed within a solid dosage form.	A system wherein a drug is incorporated into a polymer(s) structure by either particle or molecular dispersion, wherein the former is a suspension of drug particles homogenously distributed in the polymer(s) structure and in the latter drug molecules are dissolved in the polymer, and wherein drug release occurs by diffusion through and/or erosion of the polymer structure.
normal release matrix	A matrix that does not substantially slow the release of the active ingredient.	A matrix that does not slow the release of the active ingredient.
a pharmaceutically effective amount of tramadol or a salt thereof	An amount of tramadol or its salt sufficient to provide at least some analgesia.	An amount of tramadol or its salt contained in the substrate or the normal release matrix to achieve a therapeutic effect.
therapeutic effect for about 24 hours after oral administration	Effective for the treatment of one or more clinical conditions, *e.g.*, pain, for about 24 hours after oral administration.	The controlled release oral pharmaceutical preparation must cause analgesic efficacy in human patients experiencing pain as demonstrated by scientifically valid placebo-controlled clinical evidence and subsequent to oral administration of a dose of the preparation the analgesic efficacy in the patients must last for a period of about 24 hours from the time of onset of action.

ATTACHMENT A

DISPUTED CLAIM TERM	PLAINTIFFS' PROPOSED CLAIM CONSTRUCTIONS	DEFENDANTS' PROPOSED CLAIM CONSTRUCTIONS
therapeutic effect for at least about 24 hours	Effective for the treatment of one or more clinical conditions, *e.g.*, pain, for at least about 24 hours.	The controlled release oral pharmaceutical preparation must cause analgesic efficacy in human patients experiencing pain as demonstrated by scientifically valid placebo-controlled clinical evidence and subsequent to oral administration of a dose of the preparation the analgesic efficacy in the patients must last for a period of about 24 hours from the time of onset of action.